REMARKS

Claims 1, 3, 14, and 16-18 are amended. Claims 1 and 16-18 are amended to recite that the glucan does not induce a systemic release of inflammatory cytokines. Support for the amendments is found in Applicant's specification at, for example, page 44, lines 18-24.

Claims 3 and 14 are amended to correct informalities. Reconsideration and withdrawal of the rejections are respectfully requested.

The 35 U.S.C. §112, First Paragraph, Rejection

Claims 1-4, 14, 16, and 18 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action asserts that Applicant's disclosure fails to enable a skilled person to practice the claimed methods for treating types of cancer other than hepatic cancer, breast cancer, colorectal cancer, and Non-Hodgkin lymphoma. Applicant respectfully traverses the rejection.

Claims 1, 16, and 18 are independent. Each of claims 2-4 and 14 depends from claim 1 and, therefore, includes all of the features recited in claim 1. Thus, remarks that refer to claim 1, individually or collectively with one more of the other independent claims, apply equally to claims 2-4 and 14.

The Office Action analyzes claims 1, 16, and 18 with respect to the *Wands* factors and concludes that Applicant's specification fails to enable the full scope of claims 1, 16, and 18. Applicant respectfully disagrees with the analysis of the *Wands* factors and the resulting conclusion set forth in the Office Action. Applicant's analyses of the factors analyzed in the Office Action follow.

Nature of the Invention

The Office Action asserts "that the invention is complex in that it encompasses a variety of potential combinations (each of which involve a neutral soluble glucan with an anti-tumor antibody specific for a certain cancer to treat that cancer) which can collectively be used to treat tumor cells without inflammation." (Office Action, page 4). Applicant respectfully disagrees.

Claim 1 recites, in part, administering neutral soluble glucan and "at least one complement activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells" to a subject in order to suppress or eliminate tumor cells. While the identity of a particular anti-tumor antibody in any specific embodiment of the claimed method can vary, the anti-tumor antibody must be a complement activating anti-tumor antibody. Therefore, the anti-tumor antibodies encompassed within the scope of claim 1 all share a common mechanism of action, and the activity is enhanced when combined with neutral soluble glucan. The required common mechanism of action between the recited anti-tumor antibodies significantly decreases the complexity of—even simplifies—the subject matter encompassed claim 1. Thus, contrary to the conclusion set forth in the Office Action and to the extent that this *Wands* factor is non-neutral to the enablement analysis, Applicant respectfully submits that the nature of the invention recited in claim 1 weighs in favor of Applicant's specification enabling the full scope of claim 1.

Both Claims 16 and 18 recite a single anti-tumor antibody, trastuzumab. Consequently, the remarks set forth in the Office Action suggesting that the variety of anti-tumor antibodies within the scope of anti-tumor antibodies encompassed by the claims renders the claims complex cannot apply to claims 16 and 18. Thus, Applicant respectfully submits that the Specification enables the full scope of claims 16 and 18 as each claim recites a specific combination, neutral soluble glucan and trastuzumab.

Breadth of Claims

The Office Action asserts that "the claims are broad in that they encompass the suppression or elimination of tumor cells without limitation as to the tumor cell(s) to be suppressed or eliminated." (Office Action, page 4). Applicant respectfully disagrees.

With respect to claim 1, the tumor cells to be suppressed or eliminated are cells belonging to a tumor against which the complement activating anti-tumor antibody is directed. Thus, the scope of tumor cells that are suppressed or eliminated is not "without limitation" as suggested in the Office Action. Rather, the scope of tumor cells that are suppressed or eliminated are limited by the identity and target of the particular complement activating anti-tumor antibody employed while practicing the method.

Each of claims 16 and 18 expressly recites the complement activating anti-tumor antibody trastuzumab. Thus, the scope of tumor cells that are suppressed or eliminated is not "without limitation" as suggested in the Office Action. Rather, the scope of tumor cells that are suppressed or eliminated is tumor cells that belong to a tumor against which trastuzumab is directed such as, for example, metastatic mammary carcinoma and B cell lymphoma. (Applicant's specification, page 4, lines 4-7).

The Office Action further asserts that "the claims are broad in that they encompass numerous combinations of a neutral soluble glucan and an anti-tumor antibody..., which further exacerbates the complexity of the invention." (Office Action, page 4). Applicant respectfully disagrees.

Claim 1 is directed to combinations that include neutral soluble glucan and at least one complement activating antibody. Thus, the scope of claim 1 is objectively less broad than the characterization of "the claims" set forth in the Office Action—*i.e.,* not every anti-tumor antibody is necessarily complement activating. Moreover, this distinction is related to the mechanism by which the complement activating anti-tumor antibody exerts its anti-tumor effects. Consequently, the anti-tumor antibodies encompassed by claim 1 share a common mechanism of action, which is enhanced when combined with neutral soluble glucan. Thus, the scope of claim 1 is not overly broad. Moreover, as stated above with respect to the nature of the invention, the complement activating feature of the anti-tumor antibodies significantly reduces the complexity of the subject matter encompassed by the invention.

Claims 16 and 18 recite one particular anti-tumor antibody—trastuzumab. Consequently, the remarks in the Office Action regarding the claims being directed to "numerous combinations" cannot apply.

Applicant respectfully submits that the breadth of subject matter described in Applicant's disclosure is commensurate with the complement activating anti-tumor antibodies recited in claim 1. Moreover, the common mechanism of action of complement activating anti-tumor antibodies effectively simplifies the breadth of the claimed subject matter. Thus, to the extent that the *Wands* factor is non-neutral in the enablement analysis, Applicant respectfully submits that the breadth of claim 1 weighs in favor of the entire scope of claim 1 being enabled by Applicant's disclosure.

Claims 16 and 18, contrary to the assertion made in the Office Action, are not broad, but are limited to combinations that include trastuzumab. Thus, the entire scope of claims 16 and 18 is enabled by Applicant's disclosure.

Guidance of the specification

The Office Action asserts while "Applicant discloses 6 examples" of complement activating anti-tumor antibodies, no other antibodies that are directed to other tumors or tumor antigens are disclosed. (Office Action, pages 4-5). Applicant respectfully disagrees.

M.P.E.P. §2164.01 states:

> A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Thus, Applicant need not provide an exhaustive list of known exemplary complement activating anti-tumor antibodies. Applicant respectfully submits that Applicant's disclosure of the six exemplary complement activating anti-tumor antibodies adequately teaches those skilled in the art how to use complement activating anti-tumor antibodies to practice the method recited in claim 1.

Moreover, the Office Action asserts that each of the antibodies expressly described in Applicant's disclosure "is selective and specific for a single type of tumor." This statement is factually incorrect. For example, while trastuzumab is approved by the FDA for treating only a single type of tumor, it is not "specific and selective" for breast cancer tumor cells. Trastuzumab is specific for Her2/neu, which is expressed by many different types of tumor cells including, for example, B cell lymphoma cells. (Specification, page 4, lines 4-7). Applicant's examples show that three of the exemplified complement activating antibodies, 11C1, 14.G2a, and BCP-MUC1 are effective against at least <u>two different</u> types of tumors: Ptas64, a mammary carcinoma, and RMA-S lymphoma transfected with MUC1. (Specification, page 53, line 6 through page 54, line 3).

Thus, the guidance in Applicant's specification is not limited to the specific types of tumors shown in the examples, but extends to types of tumors that express antigens against which complement activating antibodies are directed.

Applicant respectfully submits that the description and examples provided in the specification involving the exemplary complement activating anti-tumor antibodies adequately conveys to one skilled in the art how other complement activating anti-tumor antibodies can be employed to practice the method of claim 1. Thus, Applicant respectfully submits that the guidance of the specification, in particular as taught by the working examples, weighs toward the entire scope of claim 1 being enabled by Applicant's disclosure.

With respect to claims 16 and 18, it is unclear why the asserted lack of disclosure of other antibodies would be considered as negatively affecting the extent to which Applicant's disclosure enables one skilled in the art to practice the methods of claims 16 and 18, each of which recites trastuzumab.

State of the art/predictability in the art

The Office Action asserts that the level of predictability in the art is relatively low. Applicant respectfully disagrees.

The Office Action asserts that it is difficult to identify antibodies that are specific for only cancer cells. (Office Action, page 5). Applicant respectfully submits that the relevance of this observation with respect to Applicant's claimed methods is unclear.

Applicant's disclosure describes enhancing the efficacy of complement activating anti-tumor antigens by combining the antibody with neutral soluble glucan. Thus, Applicant's invention is not directed to the discovery of novel tumor-specific antigens and/or antibodies that specifically bind to tumor-specific antigens. Rather, Applicant's invention exploits the novel concept that the anti-tumor activity of certain anti-tumor antibodies—*e.g.*, complement activating anti-tumor antibodies—can be enhanced when the antibody is combined with neutral soluble glucan.

Applicant's disclosure describes the enhanced anti-tumor activity observed when complement activating anti-tumor antibodies and neutral soluble glucans are combined. This resultant enhanced activity by the combination of complement activating anti-tumor antibodies

and neutral soluble glucans was not known prior to Applicant's invention. Because the underlying mechanisms responsible for the observed enhanced anti-tumor activity by the combinations expressly described in the Specification are now known, similar enhanced anti-tumor activity provided by other combinations that are not expressly described in Applicant's disclosure is entirely predictable. Applicant respectfully submits that the predictability of the art weighs toward the entire scope of claim 1 being enabled by Applicant's disclosure.

With respect to claims 16 and 18, for similar reasons cited above, these claims reciting methods comprising administering neutral soluble glucan and trastuzumab have a high level of predictability.

Amount of experimentation necessary

The Office Action asserts that it would require undue experimentation for one skilled in the art to make and use the invention as claimed. Applicant respectfully disagrees.

In reaching its conclusion, the Office Action provides no additional factual analysis, but instead reiterates the conclusions reached in each of the foregoing *Wands* factor analyses. The deficiency of each of the foregoing is specifically addressed above and, for brevity, will not be reiterated here.

In summary, Applicant respectfully submits that none of the *Wands* factor analyses apply to claims 16 and 18. Applicant further respectfully submits that the *Wands* factor analyses with regard to claim 1 were in error. Consequently, Applicant respectfully submits that claims 1-4, 14, 16, and 18 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, and request that the rejection be reconsidered and withdrawn.

The 35 U.S.C. §103 Rejection

Claims 1-4, 14, and 16-18 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Vetvicka *et al.* (*J. Clin. Invest.* 98:5-61, 1996, hereinafter "Vetvicka"), U.S. Patent No. 5,488,040 (Jamas), Hortobagyi (*Semin. Oncol.* 28:43-47, 2001), and Sliwkowski (*Semin. Oncol.* 26:60-70, 1999) as evidenced by Gelderman *et al.* (*TRENDS in Immunol.* 25;158-164, 2004, hereinafter "Gelderman"), and U.S. Patent No. 5, 221,616 ("Kolb"). Applicant respectfully traverses.

Claims 1 and 16-18 are independent. Each of claims 2-4 and 14 depends from claim 1 and, therefore, includes all of the features of claim 1. Therefore, remarks that refer to an independent claim, individually or collectively with one more of the other independent claims, apply equally to dependant claims 2-4 and 14.

Applicant respectfully submits that the Office Action fails to establish a *prima facie* case of obviousness against claims 1 and 16-18. M.P.E.P. §2141(III) states:

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn,* 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:
>
> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
>
> (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. (emphases added).

Applicant respectfully submits that the Office Action has failed to meet its burden to provide a clear articulation of reasons why the subject matter of claims 1 and 16-18 would have been obvious for one skilled in the art to combine the teachings of Vetvicka, Jamas, Hortobagyi,

and Sliwkowski, as evidenced by Gelderman and Kolb (hereinafter, "the suggested combination of documents").

Each of the rationales A-G for supporting a rejection under 35 U.S.C. §103 includes being able to reach a predictable result upon making the suggested combination ((C) "in the same way" implies predictability). Rationale (G) is the teaching, suggestion, motivation test, which must be coupled with a reasonable expectation of success in order to establish a *prima facie* case of obviousness. M.P.E.P. §2143.02. Any reasonable expectation of success is dependent upon there being sufficient predictability in the art on which the expectation can be founded. Thus, each rationale set forth by M.P.E.P. §2141 for supporting a rejection under 35 U.S.C. §103 requires, expressly or implicitly, that the suggested combination of documents provides sufficient teaching that one skilled in the art at the time the invention was made would have been able to predictably obtain the claimed subject matter.

Applicant respectfully submits that the suggested combination of documents fails to provide the required level of predictability because, at a minimum, one skilled in the art could not have administered the claimed compositions to a subject and predictably obtain the resultant enhanced anti-tumor activity compared to administering either component alone.

The Office Action cites M.P.E.P. §2144.06 and *In re Kerkhoven* (205 USPQ 1069, 1072 (CCPA 1980)) for the idea that combining two compositions, each of which is taught in the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose is *prima facie* obvious. Applicant respectfully submits that the Office Action gives an overbroad application of the cited section of the M.P.E.P. and the holding of *In re Kerkhoven*, particularly in light of *KSR*.

The facts of *In re Kerkhoven* deal with a process of combining detergents to form a detergent composition. The component detergents, when combined, do not interact or otherwise influence the action or activity of the other—e.g., they could be combined and the additive detergent effect of the combination could be reliably predicted without consideration of any capacity, competitive, or indirect influences. Under any of the factors identified by *KSR*, the combined effect of detergent combination is predictable based on knowledge of the detergent activity of each component detergent alone. The decision and rationale applied by the court is *In re Kerkhoven* is entirely consistent with *KSR* under the facts in that case.

Such is not the case in the claimed methods. In biological systems, one cannot automatically predict that two components, each of which has a known effect, can form a combined composition useful for the same purpose. The components may compete or otherwise interfere with one another so that the combination is no better than—and may be less effective than—either component by itself. Thus, the claimed methods are distinguishable from the facts on which the cited statement in *In re Kerkhoven* is based and fail to provide the predictable nature that is at the essence of each *KSR* rationale.

The fact the complement activating anti-tumor antibody and the neutral soluble glucan both activate complement to achieve their respective anti-tumor effects means that the combination may not necessarily have an additive effect. Indeed, the combination may have reduced activity compared to either component individually. If both components are acting through the same pathway, one component may saturate the pathway so that adding more of the component—or a separate component that employs the same pathway—may have no effect. Alternatively, one or both components may induce secondary effects that can limit, or even inhibit, the activity of the combination. (For example, administering certain adjuvants can induce immune tolerance rather than enhanced adaptive immunity, depending upon when the adjuvant is administered). In instances such as those involved in the claimed methods, one step in the pathway may be rate limiting so that enhancing a prior or subsequent step may have no effect. Thus, the rejection is founded on an unsupportable factual premise: that two components, each of which induces complement activation, will predictably exhibit enhanced complement activation—and the associated anti-tumor activity—if administered in combination with one another.

Prior to Applicant's disclosure, one skilled in the art could not have predicted how complement activating anti-tumor antibodies and neutral soluble glucan would interact when administered to a subject. Only after Applicant's disclosure can one skilled in the art understand the effects of administering complement activating anti-tumor antibodies and neutral soluble glucan, and extrapolate the exemplified effects to the use of other complement activating anti-tumor antibodies.

Applicant respectfully submits that the Office Action has failed to meet its burden under *KSR* to provide a clear articulation of factually supported reasons why the subject matter of

claims 1 and 16-18 would have been obvious for one skilled in the art to combine the teachings of Vetvicka, Jamas, Hortobagyi, and Sliwkowski, as evidenced by Gelderman and Kolb. Thus, Applicant submits that claims 1-4, 14, and 16-18 are patentable under 35 U.S.C. §103(a) over Vetvicka, Jamas, Hortobagyi, and Sliwkowski as evidenced by Gelderman and Kolb and respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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